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## Alcohol consumption and the risk of colorectal cancer at low levels of micronutrient intake

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### Summary

**Background:**

The purpose of our study was to assess the relationship between simultaneous exposure to alcohol and consumption of micronutrients that may have protective properties against colorectal cancer.

**Material/Methods:**

This hospital-based case-control study of colorectal cancer was carried out between January 1998 and November 1999 in Cracow, Poland. A total of 180 cases of colorectal cancer confirmed by histopathology were recruited from the University Hospital in Cracow. An equal number of controls, individually matched by gender and age ( $\pm 5$  years) were chosen from among patients from the same hospital with no history of cancer. An interviewer-administered food frequency questionnaire covering 148 food items, including the quantity consumed, was used to assess the typical dietary pattern.

**Results:**

When the analysis was carried out on quartile intake data, a consistent inverse association was confirmed between the intake of retinol, thiamine or antioxidant micronutrients (carotene, vitamin C and E) and the occurrence of colorectal cancer. Alcohol intake appeared to be an important risk factor for this cancer site, and the risk increased with the amount of pure alcohol intake. The group with deficient intake of retinol, carotene, and vitamins C and E, but with higher consumption of alcohol, incur a noticeably high risk of colorectal cancer (OR=6.79; 95%CI: 2.08–22.18).

**Conclusions:**

The data support the hypothesis that higher consumption of alcohol, when combined with low micronutrient intake, may considerably increase the risk of colorectal cancer.

**key words:**

micronutrients • retinol • thiamine • carotene • vitamin C • vitamin E

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## BACKGROUND

Colorectal cancer is one of the leading causes of death from malignancy in Poland and many other countries. Although a genetic component in the etiology of colon cancer is well established in about 10% of all cases, wide differences in cancer rates between countries and changes in rates among immigrants focus attention on diet as a potentially important factor. The specific dietary factors which may explain most of the variation in rates among countries have yet not been definitively identified, but evidence suggests that diets high in energy, animal fat, or red meat, and low in fiber, fruits, and vegetables may increase the risk of this cancer [1–3]. A higher level of physical activity is also associated with reduced risk of colorectal cancer [4–8].

Over the last ten years a considerable body of data has been assembled to identify several micronutrients that may reduce the risk of colorectal cancer. Of particular importance are ascorbic acid, dietary retinoids, carotenoids, and vitamin E, whose beneficial action may depend on their anti-oxidant effect [9–11].

Alcohol, in addition to tobacco and diet, is a major environmental factor. Numerous epidemiological studies have shown that there is a strong association between alcohol consumption and cancers of the upper aerodigestive tract and liver, pancreas and breast [3,12–15]. Some epidemiological studies have also found an association between current and past alcohol drinking and colorectal cancer, but the strength of the association at this tumor site has not been clearly established.

It is a matter of dispute whether alcohol drinkers run a higher risk of colon cancer only because they eat less vegetables and fruits that contain protective antioxidant vitamins, or whether the carcinogenic effect of alcohol is independent of dietary deficiencies. Thus the purpose of this study was to assess a hypothetical interaction involving simultaneous exposure to alcohol and consumption of micro-nutrients that may have protective properties against colorectal cancer.

## MATERIAL AND METHODS

This hospital-based case-control study of colorectal cancer was carried out between January 1998 and November 1999 in Cracow, Poland. A total of 180 cases of colorectal cancer confirmed by histopathology were enrolled from the First Surgical Clinic of the University Hospital in Cracow. An equal number of controls were chosen from among patients from the same hospital with no history of cancer, who were admitted for treatment for acute non-neoplastic conditions unrelated to digestive tract diseases. The control group was matched by age ( $\pm 5$  years) and gender to the experimental. Of the controls, 59% were admitted for cardiovascular diseases, 13% for respiratory disorders, 7% for traumatic conditions such as fractures, and 21% for acute surgical conditions. Trained interviewers using a standardized questionnaire interviewed both the study subjects and the controls. The

questionnaire included information on socio-demographic characteristics, such as:

- education and occupation;
- lifetime smoking and alcohol drinking habits;
- vocational physical activity,
- personal medical history.

An interviewer-administered food frequency questionnaire (FFQ) for 148 beverage and food items, including the quantity of each food item consumed, was used to assess the typical dietary pattern. For each food or beverage item, a commonly used unit or portion size was specified, and the participants were asked how often on the average over one year they consumed that amount of each food. The dietary interview focused on a reference period defined as beginning one year prior to a point in time 5 years before diagnosis for the patients in the experimental group, or prior to the corresponding date of hospital admission for the controls. Nutrient intakes were calculated by multiplying the consumption frequency of each unit of food by the nutrient content of the specified portion, using composition values from the Polish Institute of Nutrition [16]. The dietary portion of the questionnaire included detailed information on dietary habits relating to the following food groups:

- cereals,
- milk,
- bread,
- the spread used on bread,
- processed meats and fish,
- milk products and eggs,
- fresh fruits (summer/autumn),
- fresh fruits (winter/spring),
- meat (beef, pork),
- chicken,
- the kind of fat used for baking and frying,
- salads and fresh and cooked vegetables,
- potatoes (mashed/baked), rice or pasta,
- soups,
- sweets,
- baked goods,
- tea/coffee,
- cold drinks,
- alcoholic drinks.

The data on the frequency and amount of various alcoholic beverages was used to calculate the total consumption of pure alcohol in g/day.

## Statistical analysis

Conditional logistic regression models were used to obtain odds ratios (OR) and the corresponding 95% confidence intervals (CI) for colorectal cancer. In addition to univariate models, multiple regression analyses were applied to assess combined effects and to allow for adjustment. All results shown refer to models which included terms for education, total energy and fiber intake, and level of vocational physical activity. The percentiles of micronutrient intake refer to the distribution in the control group. Tests for trends in the quartiles of

nutrients were based on the likelihood ratio test between models with and without a linear term for the micronutrient's quartile. Median values were used to represent the quartile groups in these calculations. Nutrients were also introduced into the model as continuous variables, and the unit for every micronutrient was set as the difference between the upper cut-point of the 3rd and 1st quartiles. For more detailed cross-classifications of variables, tertiles were used. All calculations were performed with the statistical software package SAS, version 6.12, predominantly using the procedure PROC PHREG.

## RESULTS

Table 1 presents the distribution of cases and controls according to gender, age, education level, vocational physical activity, total energy and total fiber intake. Colorectal cancer cases reported a lower education level, a higher energy intake, and less physical activity related to occupation. Smoking habits were not different across the groups.

Table 2 gives the ORs of colorectal cancer by intake quartiles of various vitamins compared to the lowest as the reference level. For all micronutrients considered, except for vitamin B<sub>2</sub>, the adjusted ORs were substantially lower in persons with higher intake of vitamins. The strongest effects of higher micronutrient intake (fourth quartile) in terms of OR reduction was found for retinol (OR=0.18, 95%CI: 0.08–0.40), carotene (OR=0.20; 95%CI: 0.09–0.44) and vitamin B<sub>1</sub> (OR=0.14; 95%CI: 0.04–0.50). The ORs for colorectal cancer among high consumers of vitamin E and vitamin C were also much lower than in those with low intake. These findings are consistent with the results of the linear trend tests on the quartile values. When the micronutrients were included as continuous variables in the adjusted model, the same effects were observed. However, only the effect for retinol appeared to be significant (OR=0.54; 95%CI: 0.38–0.77).

Alcohol intake proved to be an important risk factor for colorectal cancer. The corresponding adjusted ORs for colorectal cancer for the third and fourth intake quartiles were OR=4.77 (95%CI: 1.91–11.89) and 4.54 (95%

**Table 1.** Characteristics of the colorectal cases and matched controls.

		Cases		Controls		OR	p value
		(n)	(%)	(n)	(%)		
Gender:	Males	95	52.8	95	52.8	–	–
	Females	85	47.2	85	47.2	–	–
Age:							
≤40 years		9	5.0	9	5.0	–	–
41–49		21	11.7	22	12.2	–	–
50–59		36	20.0	39	21.7	–	–
60–69		80	44.4	81	45.0	–	–
>70		34	18.9	29	16.1	–	–
Education: (age at which education was terminated)							
≤15 years		35	19.4	42	23.3	1.0	–
>16		145	80.6	138	76.7	1.29	0.35
Vocational physical activity:							
Not working		83	46.1	74	41.1	1.0	–
Light work in sitting or standing position		65	36.1	59	32.7	0.91	0.73
Moderate and heavy manual labor		32	17.8	47	26.1	0.54	0.06
Total energy intake: (in quartiles)							
1 <sup>st</sup> quartile (low)		22	12.2	45	25.0	1.0	–
2 <sup>nd</sup>		27	15.0	45	25.0	1.22	0.57
3 <sup>rd</sup>		51	28.3	45	25.0	2.21	0.02
4 <sup>th</sup> quartile (high)		80	44.4	45	25.0	3.61	0.0001
Total fiber intake: (in quartiles)							
1 <sup>st</sup> quartile (low)		40	22.2	45	25.0	1.0	–
2 <sup>nd</sup>		23	12.8	45	25.0	0.59	0.13
3 <sup>rd</sup>		49	27.2	45	25.0	1.22	0.53
4 <sup>th</sup> quartile (high)		68	37.8	45	25.0	1.56	0.12
Smoking:							
Never smokers		87	48.3	74	41.1	1.0	–
Ex-smokers		62	34.4	64	35.6	0.79	0.36
Current smokers		31	17.2	42	23.3	0.58	0.08
Alcohol intake g/day (in quartiles)							
1 <sup>st</sup> quartile (low)		24	13.3	45	25.0	1.00	–
2 <sup>nd</sup>		24	13.3	45	25.0	1.14	0.72
3 <sup>rd</sup>		76	42.2	45	25.0	5.39	0.0001
4 <sup>th</sup> quartile (high)		56	31.1	45	25.0	4.76	0.0005

**Table 2.** Estimates of the adjusted\* odds ratios (ORs) and 95% Confidence Intervals for colorectal cancer by quartile intake of selected nutrients.

Nutrients	Intake Quartiles				X <sup>2</sup> trend	Continuous OR (95% CI)
	1 <sup>st</sup>	2 <sup>nd</sup>	3 <sup>rd</sup>	4 <sup>th</sup>		
Retinol (mg/day)	<0.60**	0.60–0.83	0.84–1.43	≥1.44	16.83	
	1.00	0.34	0.51	0.18	p<0.001	0.54
	–	(0.16, 0.71)	(0.25, 1.04)	(0.08, 0.40)		(0.38–0.77)
Carotene (mg/day)	<2.10	2.10–2.58	2.59–3.28	≥3.29	23.96	
	1.00	0.12	0.19	0.20	p<0.001	0.93
	–	(0.05, 0.28)	(0.09, 0.40)	(0.09, 0.44)		(0.82–1.07)
Vitamin E (mg/day)	<7.34	7.34–8.69	8.70–10.59	≥10.60	4.25	
	1.00	0.40	0.44	0.44	p<0.039	0.98
	–	(0.15, 0.66)	(0.21, 0.88)	(0.21, 0.92)		(0.89–1.08)
Vitamin B <sub>1</sub> (mg/day)	<0.81	0.81–0.94	0.95–1.16	≥1.17	8.50	
	1.00	0.44	0.25	0.14	p<0.01	0.92
	–	(0.18, 1.10)	(0.09, 0.73)	(0.04, 0.50)		(0.73–1.16)
Vitamin B <sub>2</sub> (mg/day)	<1.05	1.05–1.27	1.28–1.57	≥1.58	0.29	
	1.00	1.04	1.40	1.27	p=0.59	1.29
	–	(0.45, 2.43)	(0.61, 3.18)	(0.50, 3.27)		(0.94–1.79)
Vitamin C (mg/day)	<63.6	63.61–79.81	79.82–94.05	≥94.06	13.95	
	11.00	0.44	0.17	0.33	p<0.001	0.87
	–	(0.22, 0.90)	(0.08, 0.40)	(0.16, 0.71)		(0.71–1.05)

\* – adjusted by energy intake, total fiber intake and vocational activity;

\*\* – information in each cell: 1<sup>st</sup> line: range of quartile; 2<sup>nd</sup> line: Odds Ratio; 3<sup>rd</sup> line: 95% Confidence Interval

CI: 1.56–13.20), with a significant trend test ( $\chi^2=7.19$ ,  $p<0.01$ ). The effect of alcohol was also significant after alcohol intake was entered in the model as a continuous variable (OR=1.31, 95%CI: 1.07–1.60).

The effects of vitamin intake and alcohol consumption on the occurrence of colorectal cancer were assessed separately for each vitamin in multiple logistic models, where the effects of both factors were adjusted to confounders (education, vocational physical activity, total energy, and total fiber intake). The results of this latter analysis, presented in Table 3, demonstrate that at each level of retinol intake there was a clear and consistent OR trend for colorectal cancer with a higher amount of alcohol consumption. By contrast, at each alcohol consumption level there was a consistent reduction of ORs for colorectal cancer with a higher vitamin intake. The same pattern was also observed for carotene, vitamin C, vitamin B<sub>1</sub>, and vitamin E. In the strata with high vitamin intake, however, the excess of colorectal cancer risk due to alcohol intake was not significant. The interaction terms did not appear to be statistically significant in either of the analyses (results not shown). The consistent inverse relation between vitamin intake and colorectal cancer due to alcohol consumption suggest a protective effect at higher levels of vitamin intake.

In the final stage of the analysis, we considered the adjusted ORs of colorectal cancers for combined micronutrient intakes. Subjects were classified into three major categories: low intake was defined as retinol, carotene, vitamin C and vitamin E intake below the median values for each of them, subjects with intake above the medians for each vitamin were placed in the high intake category, while the rest were assigned to the mixed category. ORs were estimated from multiple logistic regression using the same set of confounders

(Table 4). It turned out that the group with low micronutrient intake but higher alcohol consumption incurred a remarkably high risk of colorectal cancer (OR=6.79; 95%CI: 2.08–22.18), but among those who reported a higher intake of micronutrients the risk was insignificant (OR=1.35; 95%CI: 0.39–4.67).

## DISCUSSION

Our study, the first in Poland on dietary habits and colorectal cancer, has confirmed the protective effect of higher intake of retinol and antioxidant vitamins for the occurrence of colorectal cancer, when the analysis is carried out on quartile intake data. This was then confirmed in a multivariate analysis done on micronutrients as continuous variables. Retinol intake showed the strongest OR trend. The protective effect of antioxidant vitamins C and E or carotenoids against cancer has been confirmed by many studies [1–3,12–15]. Furthermore, our results demonstrated the preventive effect of retinol and thiamine (vitamin B<sub>1</sub>) as well. Inverse correlation between thiamine and colon cancer has recently been reported by Slattery et al. [3].

Our data confirmed the evidence that alcohol consumption is an important risk factor for colorectal cancer. However, it was shown that the effect of alcohol needs to be assessed in combination with the micronutrient intake level. Both factors were shown to act as independent risk factors for colorectal cancer. Some of the increased risk reported in the literature and attributed to this factor may result from lower intake of retinol and antioxidant micronutrients in subjects with higher alcohol consumption. The associations observed for alcohol and micronutrients were not due to confounding by smoking, education level, vocational physical activity or total energy and fiber intake. The high consistency with-

**Table 3.** Effect of alcohol consumption on colorectal cancer risk by tertiles of retinol intake. ORs and 95%CI estimated from a multiple logistic model with adjustment for education, vocational physical activity, total energy and fiber intake.

Vitamin intake mg/day (in tertiles)	Tertiles of alcohol consumption (g/day)			Total
	1 (low) 0–3.6	2 (medium) 3.6–14.2	3 (high) ≥14.2	
Retinol				
1 (low)	1.00	2.32	4.74	1.00
0–2.22	–	0.78–6.93	1.34–16.69	–
2 (medium)	0.57	1.70	2.36	0.61
2.22–2.99	0.20–1.62	0.53–5.43	0.68–8.18	0.34–1.11
3 (high)	0.26	0.73	1.16	0.31
≥2.99	0.06–1.14	0.21–2.52	0.33–4.12	0.16–0.60
Carotene				
1 (low)	1.0	1.35	2.30	1.00
0–2.28	–	0.38–4.72	0.62–8.52	–
2 (medium)	0.01	0.44	0.75	0.19
2.28–2.97	0.01–0.17	0.09–2.30	0.19–2.99	0.10–0.38
3 (high)	0.10	0.51	0.71	0.28
≥2.97	0.02–0.56	0.15–1.72	0.17–2.97	0.14–0.54
Vitamin B <sub>1</sub>				
1 (low)	1.0	1.15	4.54	1.00
0–0.84	–	0.33–4.05	1.15–17.91	–
2 (medium)	0.23	1.40	1.37	0.51
0.84–1.07	0.06–0.85	0.37–5.29	0.36–5.29	0.23–1.14
3 (high)	0.36	0.50	0.57	0.29
≥1.07	0.07–1.76	0.12–1.98	0.12–2.61	0.11–0.80
Vitamin C				
1 (low)	1.00	1.54	2.32	1.00
0–66.05	–	0.48–4.89	0.67–7.98	–
2 (medium)	0.04	0.67	0.71	0.25
66.05–85.11	0.01–0.28	0.18–2.38	0.18–2.78	0.13–0.50
3 (high)	0.12	0.42	0.84	0.28
≥85.11	0.03–0.56	0.12–1.51	0.22–3.28	0.14–0.55
Vitamin E				
1 (low)	1.0	0.97	2.32	1.00
0–7.75	–	0.31–3.06	0.64–8.42	–
2 (medium)	0.1	1.18	0.79	0.39
7.75–10.05	0.02–0.44	0.32–4.43	0.21–2.97	0.20–0.78
3 (high)	0.38	0.70	1.05	0.48
≥10.05	0.11–1.40	0.19–2.52	0.27–4.09	0.25–0.92
Total	1.00	2.58	3.70	
	–	1.14–5.85	1.38–9.92	

in our data strengthens the internal validity of our study. Four combined factors (retinol, vitamin C, carotene, and vitamin E) reduce the alcohol-related risk of colorectal cancer, though in the separate analyses the association was strongest for retinol. It is noteworthy that alcohol was related to colorectal cancer risk only if the intake of micronutrients was deficient. Thus it is reasonable to assume that moderate consumption of alcohol in conjunction with high antioxidant micronutrients may not substantially increase the risk of colon cancer.

Our data on the alcohol-related risk of colorectal cancer is in good general agreement with many case-control and prospective studies [17–23]. A review of studies on alcohol consumption and colorectal cancer in humans done by Kune et al. [14] demonstrated that over the last 35 years there were 52 major studies. Elevated risk has

been reported in about half of the 31 case-control studies, and 10 out of 14 cohort studies. There are several possible explanations for the conflicting results, such as the small numbers of cases in some studies, the use of hospital controls whose diagnoses could have included alcohol-related diseases, different methods of assessing intake, and the quality of data on alcohol use. Furthermore, in studies on alcohol, different approaches were used in measuring exposure variables. In our study, for example, alcohol consumption was defined in terms of pure alcohol intake.

On the other hand, the inconsistencies among the various studies may result from the fact that in many studies the antioxidant micronutrient intake was not accounted for. Our data demonstrated that the lower availability of these micronutrients increases the risk of colorectal cancer, because they mitigate the influence of alcohol.

**Table 4.** Adjusted\* ORs and 95% Confidence Intervals for colorectal cancer by combined levels of all micronutrients\*\*.

Micronutrients Intake level**	Alcohol intake		Total
	Lower level (0–5.6 g/day)	Higher level 5.6> g/day	
Low	1.00	6.79	1.00
	–	2.08–22.18	–
Medium	0.61	2.47	0.49
	0.23–1.63	0.88–6.99	0.25–0.98
High	0.52	1.35	0.29
	0.12–2.29	0.39–4.67	0.12–0.71
Total	1.00	4.42	
	–	2.10–9.31	

\* Adjusted for education, total energy and total fiber intake, occupational physical activity; \*\* Combined micronutrient level defined via median cut-off points: Low: subjects with the intake value of each micronutrient below the median; High: subjects with an intake value above the median for each micronutrient, Medium: subjects with neither a low nor a high intake, i.e., mixed intake. Median values for retinol =0.83, vit.C =80.0, vit E =8.7 and carotene =2.6, alcohol= 5.6 g/day

Various dietary patterns among populations may modify the risk associated with alcohol, and thus contribute to the apparent inconsistencies among studies.

Despite the large body of epidemiological evidence, alcohol in itself has not been proven to be directly carcinogenic. It seems unlikely that the small concentrations of alcohol reaching the bowel mucosa would have much direct effect. However, there are several plausible mechanisms by which alcohol intake may increase the risk of colorectal cancer. First, alcohol may alter the metabolism of large bowel carcinogens in the liver, an effect that has been demonstrated in animal models. Secondly, the composition of bile is altered by alcohol consumption, and bile composition is suspected of being linked to colorectal carcinogenesis. Thirdly, alcohol may change the rate of epithelial proliferation in the large bowel, an effect that may be related to carcinogenesis. Other possible mechanisms involve alcohol-induced impairments of cellular DNA repair mechanisms, increased intracellular peroxidation, or immune system depression [2,10].

Our findings on the very strong inverse association between retinol intake and colorectal cancer suggest that deficient intake of retinol in alcohol drinkers may be of importance in understanding carcinogenic processes. Vitamin A (retinol) regulates epithelial differentiation by conversion to retinoic acid. Moreover, the inhibition of retinoic acid synthesis by ethanol in the ADH (acetaldehyde) step may lead to the accumulation of acetaldehyde, which is assumed to be a possible candidate for carcinogenesis. Acetaldehyde easily reacts with cellular components and induces cytotoxicity [24–27].

The most important suggestion from our study is that high alcohol consumption, when combined with low intakes of retinol and antioxidant vitamins, may considerably increase the risk of colorectal cancer. However,

exposure to alcohol may be a necessary but not sufficient condition for colon cancer. Low vitamin intake or low intake of other micronutrients may be a component in the sufficient condition. This interpretation is biologically plausible, since dietary micronutrients are of essential importance in modulating the risk of cancer at selected body sites, as has been demonstrated by various epidemiological observations.

## CONCLUSIONS:

1. The protective effect of retinol and antioxidant vitamins against the occurrence of colon cancer depends on the intake level.
2. Our data suggest that alcohol consumption may be an important risk factor for colorectal cancer, but its effect is manifested at low levels of micronutrient intake.

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